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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,697	07/25/2001	Nicholas C. Nicolaides	MOR-0040-	5193

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EXAMINER

LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/912,697

Applicant(s)

NICOLAIDES ET AL.

Examiner

Zachariah Lucas

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3,14-25,27,38 and 42 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,14-25,27,38 and 42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Status of the Claims*

1. Claims 1, 3 14-25, 27, 38, and 42 are pending in the application. Claims 1, 3, 14-25, 27, 38, and 42 are under consideration to the extent that they read on the elected invention.

2. In the prior action, mailed on October 20, 2003, claims 1, 3, 14-25, 27, 38, and 42 were rejected. In the Response to that action, received by the Office on April 20, 2004, the Applicant cancelled claims 4-13, 28-37, and 39-41.

### *Claim Rejections - 35 USC § 103*

3. **(Prior Rejection- Maintained)** Claims 1, 3, 15, 27, and 38, and 42 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Nicolaides 1 (U.S. Pre-Grant Publication 2002/0068284). The Applicant traverses this rejection by asserting that the Nicolaides 1 reference does not teach that the hypermutable mutation of the bacteria may be used to develop bacteria with multiple antibiotic resistances, but is limited to teaching the use of such mutation to derive bacteria with a single desired trait. This argument is not found persuasive. As was indicated in the prior action, the reference teaches that the hypermutable bacteria used in the application may be used to “screen for novel *mutations* ... that produce variant siblings that exhibit a *new output trait(s)* not found in the wild type cells.” Page 3, paragraph 0029 (emphasis added). This language indicates that the bacteria may be used to produce cells with one *or with multiple mutations and traits*. In view of these teachings, the Applicant’s arguments are not found persuasive, and the rejection is maintained.

4. **(Prior Rejection- Maintained)** In the prior action, claims 1, 19, 27, and 38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Iris (U.S. Patent 6,221,585) in view of Stemmer (U.S. Pub 2001/0049104) and Johnston (U.S. Patent 6,043,048), in view of Aronshtam et al. (Nucleic Acids Research, 24(13): 2498-2504), and further in view of the teachings of LeClerc (Science 274: 1208-11), Drummond (J Biol Chem, 271: 19645-48), and Moreland (Cancer Research, 59:2102-04), and Morris et al. (J Infect Dis 171: 954-60). The Applicant traverses the rejection by asserting that there is no motivation to combine the indicated reference, and that there is no reasonable expectation of success that such a combination would result in the claimed methods and bacterium.

The Applicant's first argument in traversal of this rejection again focuses on the difference between the teachings of the Iris and Stemmer references. The Applicant argues that these references are "completely polar approaches to identify genes associated with a phenotype" and that those in the art would therefore not think to combine their teachings. However, these references are not cited to combine their teachings with reference to the modes of operation, but to demonstrate that those in the art would look to the differences in genetic makeup with reference to target phenotypes as a basis for the development of disease therapies. Thus, while the modes of identification among these references are different, the teachings of both of these references point to the identification of genetic mutations in developing disease therapies. These references are cited to demonstrate motivation to study the relationship between genetic and phenotypic traits. Such a motivation, when combined with the suggestion of the other references to study the source of anti-biotic resistance, and the use of defective mismatch repair to induce

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phenotypic change, would result in motivation to perform the claimed methods and made the claimed bacterium for the purpose of developing better drugs against the bacterium.

Applicant's assertions on page 8 of the Response regarding the teachings of Stemmer and Aronshtam are noted. However, in response to Applicant's assertion that Stemmer nowhere teaches the use of defective mismatch repair to induce phenotypic variation, the Applicant's attention is drawn to page 12, paragraph [0119], cited in the first action on the merits. This suggestion, in combination with the teachings of Aronshtam provides adequate motivation to use defective mismatch repair to induce mutations in an organism. The citation of LeClerc, Drummond, and Moreland, as noted in the prior action, merely demonstrate that those in the art were aware of the fact that defective mismatch repair has been known to result in mutations leading to cellular resistance to drugs. They are not intended, alone, to suggest the use of such to make antibiotic resistant bacterium. However, when combined with the teachings of the other references, they do provide grounds for those in the art to have a reasonable expectation of success in the making of anti-biotic resistant bacterium upon suggestion by the other reference to do so.

In each remaining instance where the Applicant asserts that some aspect of the claimed invention is not taught, the Applicant considers the teachings of only a few of the references. Such piecemeal consideration is not sufficient to overcome a rejection based on the totality of the teachings. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, the Applicant's assertion that there is insufficient motivation to combine the teachings is not found persuasive.

The second argument is that there is no expectation of success in the combination of the references. In particular, the Applicant asserts that the Johnston reference does not teach the making of multi-antibiotic resistant bacterium. While the Examiner agrees that this is the case, the reference is not asserted to teach such. The reference demonstrates that it is known how to screen for antibiotic resistant phenotypes in bacteria. Further, as noted by the Applicant, Morris teaches that such multi-antibiotic resistance results from a build-up of multiple mutations. The rate of mutation of a cell line is also indicated by the art to increase with the presence of a defective mismatch repair system. See e.g., LeClerc (stating that mutations leading to defective mismatch repair “increase the mutation rate” of cells). From these teachings, indicating that a build-up of mutation results in the generation of multi-antibiotic resistance, and the teachings of LeClerc that defective mismatch repair increases the rate of mutation, those in the art would have had a reasonable expectation of success in using the claimed method to derive a multi-antibiotic resistant bacterium. The Applicant’s second argument is also not found persuasive.

The Applicant additionally traverses the rejection of claim 27 by asserting that, without support in the art, those in the art would not have been motivated to stabilize multi-antibiotic resistant bacterium once a desired phenotype had been isolated. However, as was noted by the Applicant, the Examiner has provided a rational and scientific argument as to why it would be obvious in the prior art. Such a rationale, when based on knowledge that was generally available to those in the art, is sufficient to render a claimed invention obvious. See MPEP § 2144 (stating that rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, and

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citing case law support therefore). In contrast, the Applicant has presented no argument or evidence that it would not have been obvious. Whereas the Office action has the support rationale for obviousness based on the generic teachings of the art, the Applicant's traversal is no more than an unsupported assertion to the contrary. The traversal is therefore not found persuasive.

The rejection is therefore maintained for the reasons above, and the reasons of record.

5. **(Prior Rejection- Maintained)** Claims 1, 3, 27, 38, and 42 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Iris in view of Stemmer and Johnston as applied to claims 1, 2, 27, and 38 above, and further in view of either Nicolaides et al., Molecular and Cellular Biology, 18(3): 1635-1641 (Nicolaides 2) or Nicolaides et al., U.S. Patent 6,146,894 (Nicolaides 3) and of LeClerc, Drummond, Moreland, and Morris. The Applicant traverses this rejection on substantially the same grounds as presented above with respect to the teachings of the Stemmer reference. For the reasons indicated above, that Stemmer does suggest the use of defective mismatch repair to induce genetic change and diversity, the Applicant's traversal is not found persuasive.

6. **(Prior Rejection- Maintained)** Claims 1, 3, 14-25, 27, 38, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of 1) Iris, Stemmer, Johnson, in view of Aronshtam; or 2) Iris, Stemmer, Johnston and either or Nicolaides 2 or 3, and in view of LeClerc, Drummond, Moreland, and Morris and further in view of Lin (U.S. Patent 6,025,400, column 1), Chang et al. (U.S. Patent 6,043,220, column 1), Setterstrom et al. (U.S. Patent

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6,410,056, column 4), and The Merck Index, (1983, pages 2036, 5032-33, and 6448-449) as presented in the prior action. The Applicant traverses the rejection on the grounds presented above, and on the grounds that the references do not specifically teach or suggest the development of multi-antibiotic resistant bacterium with resistance to each of the antibiotics identified in the claims. The arguments not based on the individual antibiotics have been addressed above. These arguments have not been found persuasive.

The traversal on the grounds that the art does not explicitly suggest or teach developing bacteria resistant to the indicated compounds is also not found persuasive. As was indicated above, and in the prior actions, the Iris and Morris references provide motivation for the development of such bacterium. I.e. to provide further insight and to help in the development of more effective anti-bacterial treatments. From these teachings, it would have been obvious to those in the art to develop bacterium with resistance to any of the known antibiotics. The rejection is therefore maintained.

### ***Conclusion***

7. No claims are allowed.
8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period


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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Z. Lucas  
Patent Examiner

  
JAMES HOUSEL 7/26/04  
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